

Docket No.: IBIS-0007 Filed: May 12, 1998 076,404 lation of Molecular Interaction Sites on RNA and Other Biomol Inventors, ricker et. al. Attorney: Jeffrey H. Rosedale Phone: (215) 568-3100 Sheet 1 of 59

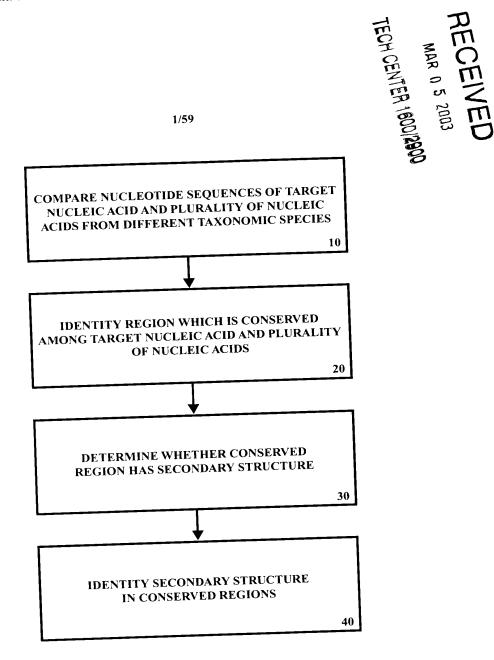
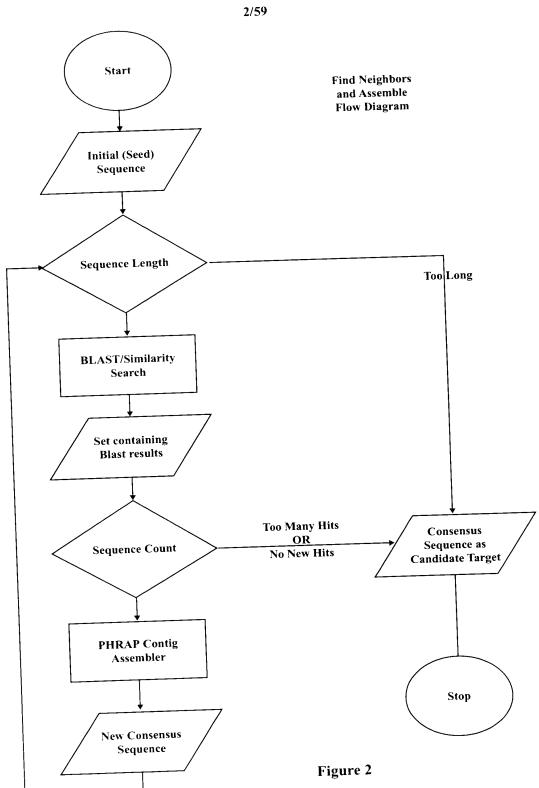


FIGURE 1





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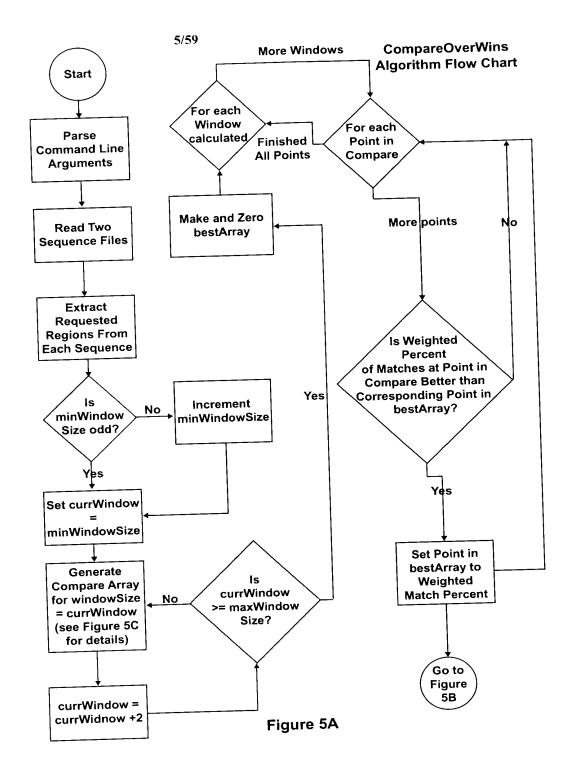
Modulation of Molecular Interaction Sites on RNA and Other B

Inventors: Ecker et. al.

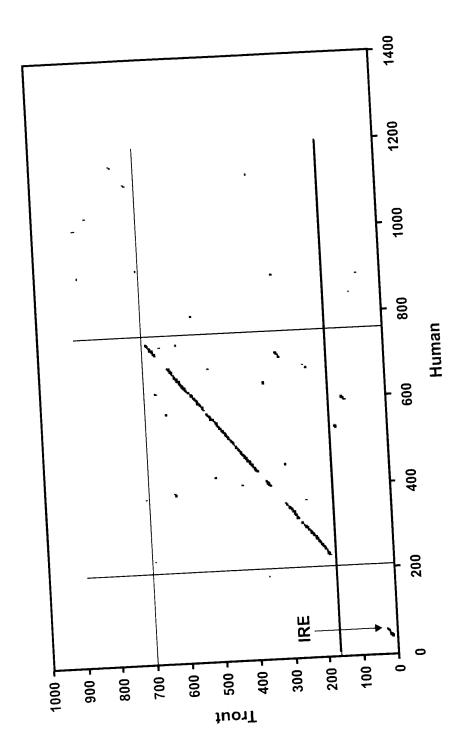
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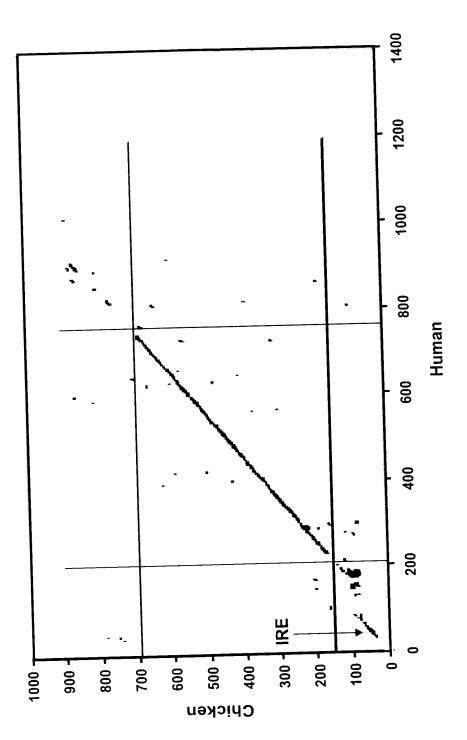


Figure 12

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G-U G C C C C C C C C C C C C C C C C C C	YES	YES	YES	YES	ON			
G-U A-U A-U C-G U-A U-A U-G U-G U-G SALMON	YES	YES	YES	O _N				
G-U A-U C-G U-G G-C G-C C-G C-G	YES	YES	ON					
G-U A-U A-U C-G U-A U-G C-G C-G D-A D-A D-A D-A D-A D-A D-A	S 0	ON						
G-U A-U A-U C-G C-G C-G C-G	ON							
	HUMAN	HAMSTER MOUSE	RAT	TROUT	SALMON	FROG	FLY	MOSQUITO

Figure 13

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Compound CI

 $C_{12}H_{18}N_2O_5S$

$$\begin{bmatrix}
H \\
HO
\end{bmatrix}$$

$$\begin{bmatrix}
H_3C \\
CH_3
\end{bmatrix}$$

$$\begin{bmatrix}
O \\
S \\
O \\
O \\
H
\end{bmatrix}$$

$$O CH_3$$

$$F_{ii}$$

$$F_{iii}$$

Molecular Formula

H₂NO C₅H₉NO

 $C_7H_7O_3S$

Figure 14

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Addition of fragments to yield compounds

	Table						
Fragment Identifier	Structure	Name	Molecular formula	Other			
Fi	H-O-N-	Hydroxylamine	H ₂ NO				
F _{ii}	H ₃ C CH ₃	Amino acid	C₅H ₉ NO				
F _{iii}	-\$	c _{H3} Sulfonyl	C ₇ H ₇ O ₃ S	•••			

Figure 15

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Reagents	Identifier	Name	Properties	
$H^-O^-NH_2$ or $P^-O^-NH_2$	R _i	Hydroxylamine		
H ₃ C CH ₃ HO N-FMOC	R_{ii}	FMOC blocked amino acid		
CI-S O OCH ₃	R _{iii}	Sulfonylchloride		
P = solid support				

Figure 16



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Transformation

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Figure 17



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Common Fragment/Different Reagents and Transformations

Figure 18



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Common Fragment/Different Reagents and Transformations

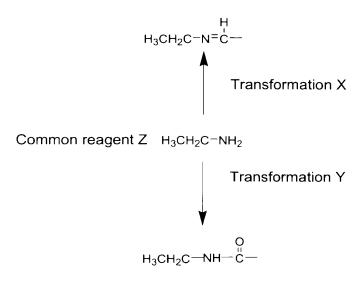


Figure 19A



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Common Reagent

$$\begin{array}{c|c} & H_3C & \frown_{CH} - \\ & & \\ &$$

Figure 19B



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Symbolic addition of fragments to yield compound

Symbolic Structure	Symbolic Identifier	Molecular formula
Fragment		
$\sum x$	$\mathbf{F_{i'}}$	$C_uH_vN_w$
<u> </u>	F _{ii'}	$C_uH_vN_w$
x −○− Y	$\mathbf{F_{iii'}}$	$C_uH_vN_w$
Compound		
	CI'	$C_uH_vN_w$
		Molecular formula F _{i'} +
		Molecular formula F _{ii'} +
		Molecular formula Fiii'
		= Molecular formula CI'

Figure 20



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Symbolic Reagent Table

Identifier	Name	Structure	Molecular formula
R1	xxx	∠ CI	xxx
R2		CNO	
R3	•••	CI	
R4		Br	
R5		□ Br □ Br	
R6		Pg—O—OEt	
R7		Pg——CI	
R8	•••	Pg——Br	
R9		Pg1 N3 — Pg2	
R10		Pg1 N3	

Figure 21



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Symbolic Fragment Table

Identifier	Symbolic Sturcture	Molecular Formula	Molecular Weight
F1	∠ X	xxx	xxx
F2	<u></u> -х		
F3	○ -x		
F4	x x		
F5	X—O—Y		
F6	X——Y		
F7	x − z		
F8	x Z z		



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Symbolic Transformation Table

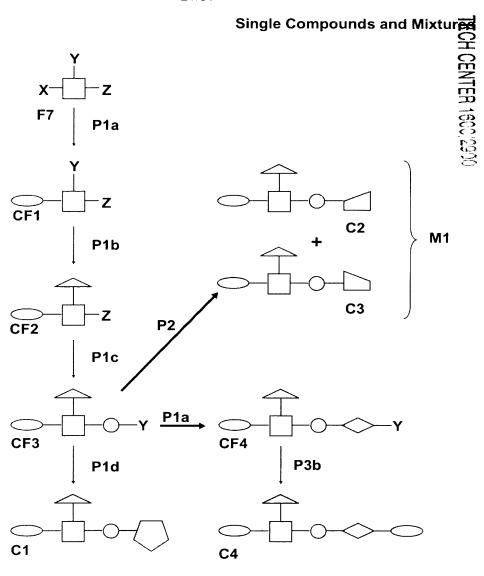
<u>Identifier</u>		Symbolic Re	actions		Reagent
T1	F1	X	4	R1	conditions α
T2	F2	<u></u> х	←	R2	$\textbf{conditions} \ \boldsymbol{\beta}$
Т3	F3	○ -x	←	R3	conditions α
Т4	F3	○ -x	•	R4	conditions α
Т5	F4	x x	4	R5	conditions α
Т6	F5	X—O—Y		R6	conditions $\boldsymbol{\epsilon}$
Т7	F5	X—O—Y		R7	conditions $\boldsymbol{\alpha}$
Т8	F6	X——Y		R8	conditions α
Т9	F7	x-L-z	4	R9	conditions γ
T10	F8	$x \stackrel{Y}{\triangleright}_{z}$	-	R10	conditions γ

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P = synthetic path

CF = complex fragment

F = fragment

M = mixture

C = compound

Figure 24



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Mixture 2

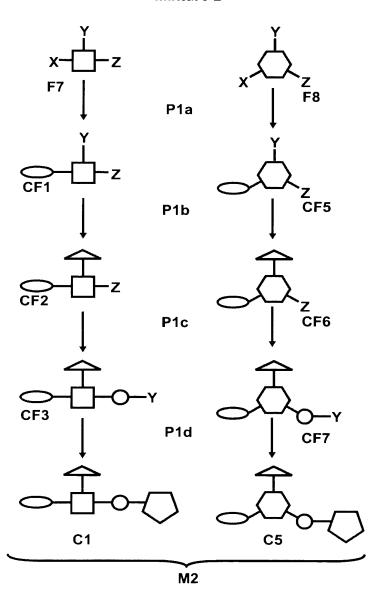


Figure 25



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Mixture 3

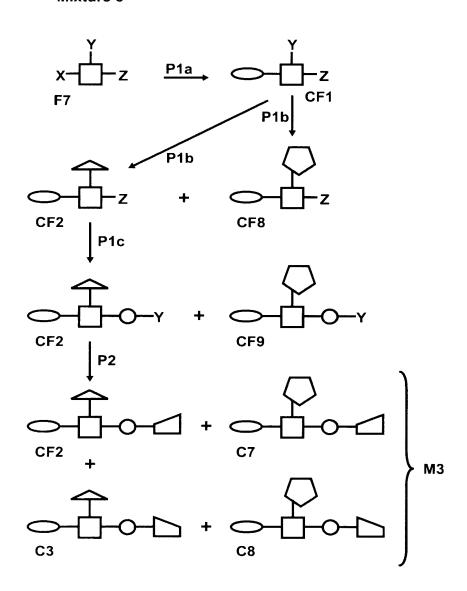


Figure 26



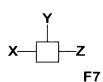


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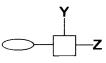


2 Starting Fragments

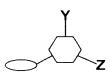


F8

2 Complex Fragments

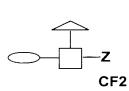


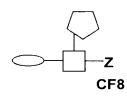
CF1

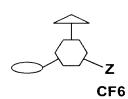


CF5

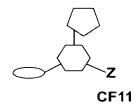
4 Complex Fragments





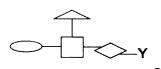


CF9



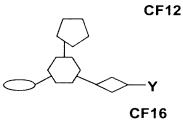
8 Complex Fragments

CF3



CF13

CF15



CF7

CF14

Figure 27A



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Mixture 4 (continued)

16 compounds

Figure 27B



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Tracking Table for Compound C1

(a) By Fragments:

n	n+1	n+2
F7		
	F2	
	F1	
	F5	
		F3

(a) By Transformations:

Syn	Synthesis Path 1		Synthesis Path 2				
n	n+1	n+2		n	n+1	n+2	
Т9			,	Т9			
	T2				T2		
	T1				T1		
Ì	T6				T7		
		T3				T3	
Syr	Synthesis Path 3			Syn	thesis P	ath 4	
n	n+1	n+2		n_	n+1	n+2	

			•		
n+1	n+2		n_	n+1	
			Т9		
T2				T2	
T1				T1	
Т6				T7	
	T4				
	T2 T1	T2 T1 T6	T2 T1 T6	T2 T1 T6	T2 T2 T1 T1 T7

Figure 28

T4



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Tracking Table

Tracking M1

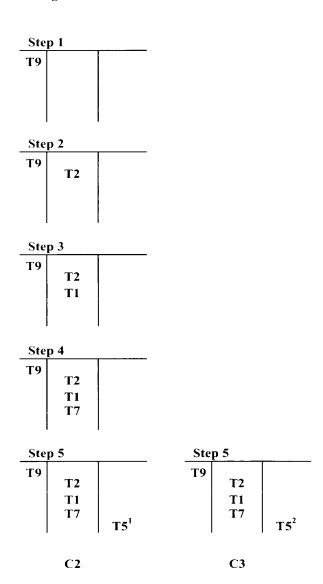


Figure 29



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Tracking Table

Tracking M2

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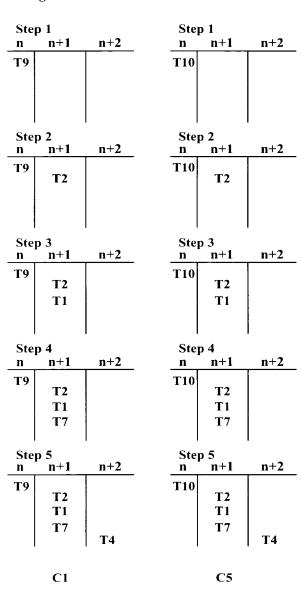


Figure 30



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Tracking Table

C2

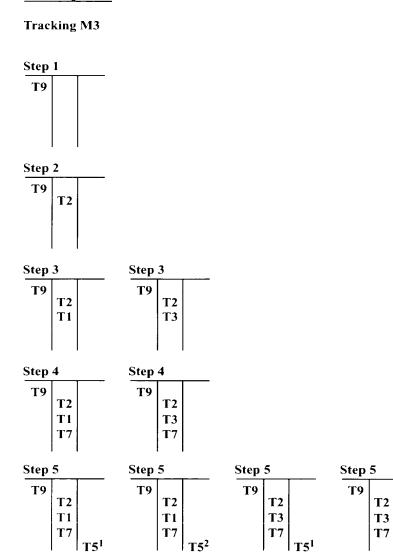


Figure 31

C7

C3

 $T5^2$

C8

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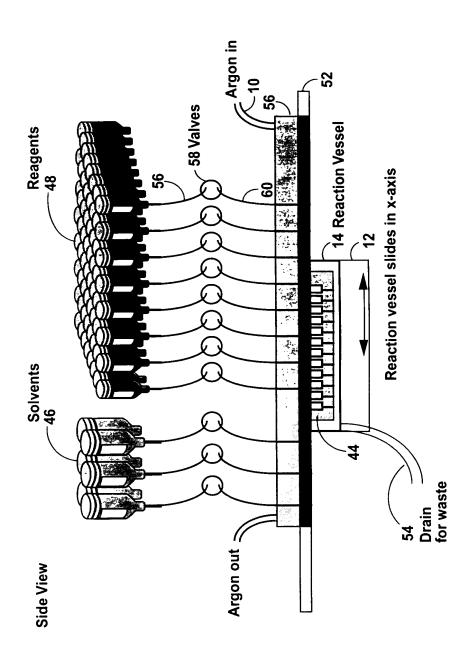


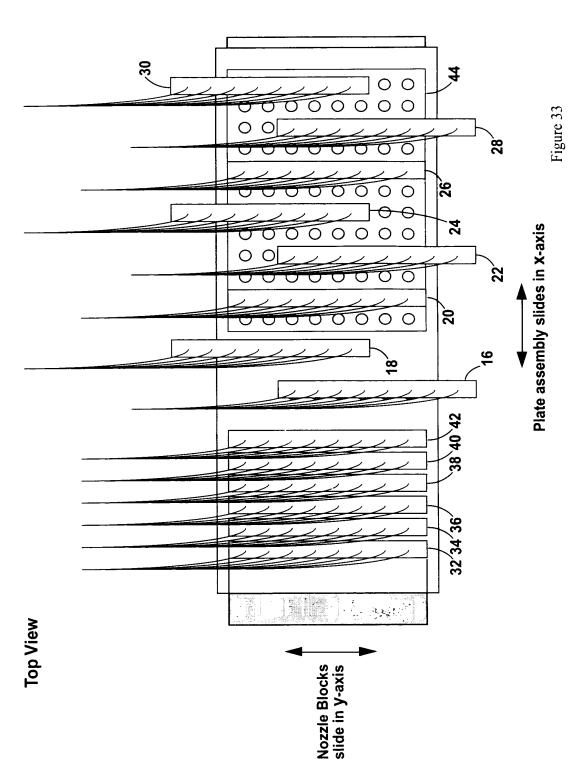
Figure 32



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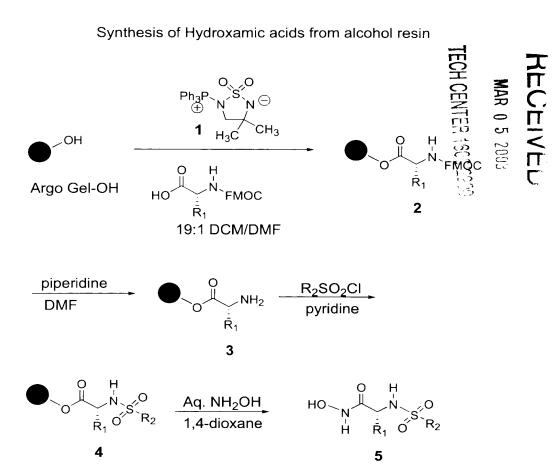


Figure 34



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Synthesis of hydroxylamine resin

Figure 35



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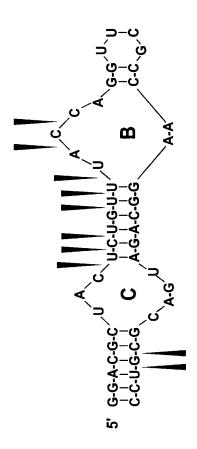
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IС₅₀ (µМ) < 50 Calc. ∆G of binding (kcal/mole) -8.5 -5.1 -5.1 0=8-0 Structure ACD Code 00192509 00003934 00001199

Figure 37



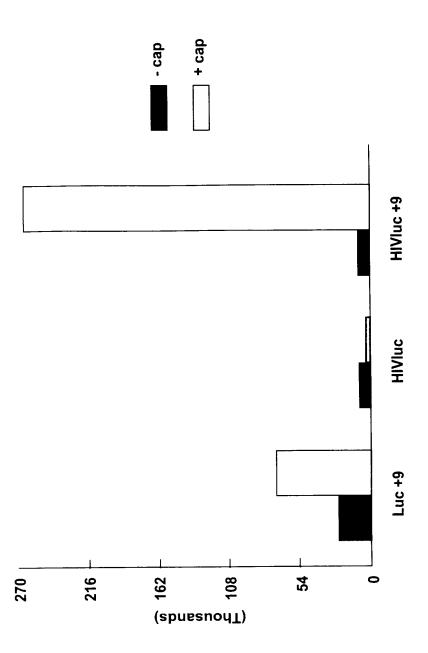


Figure 38A

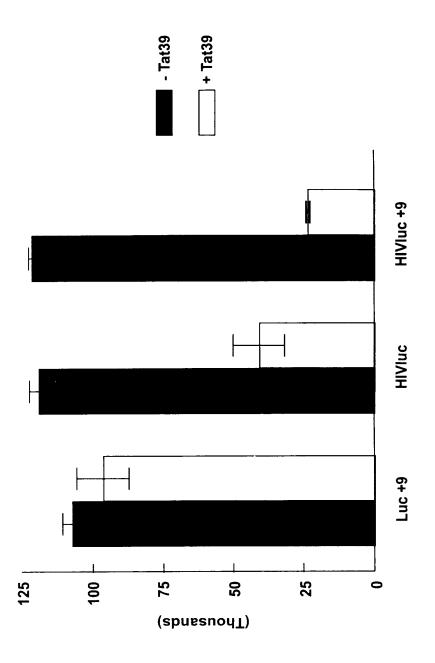
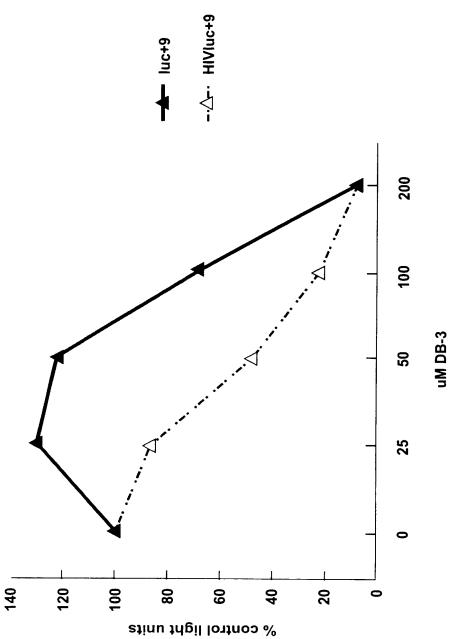


Figure 38B

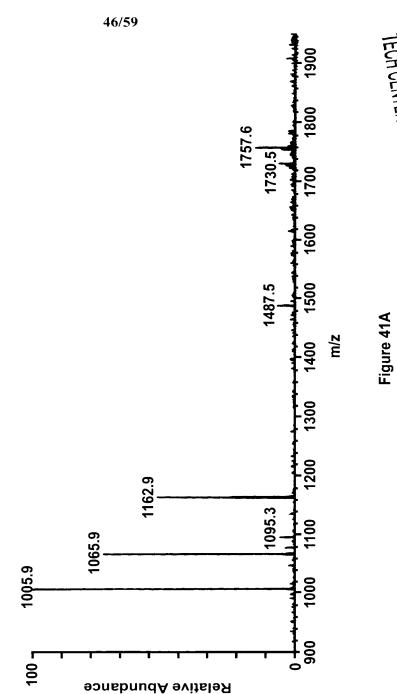


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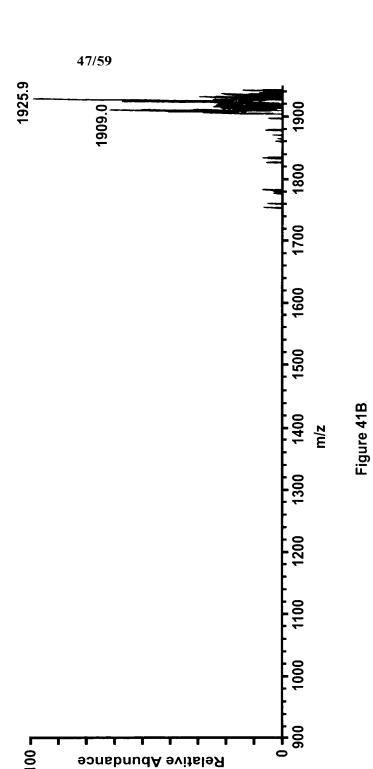
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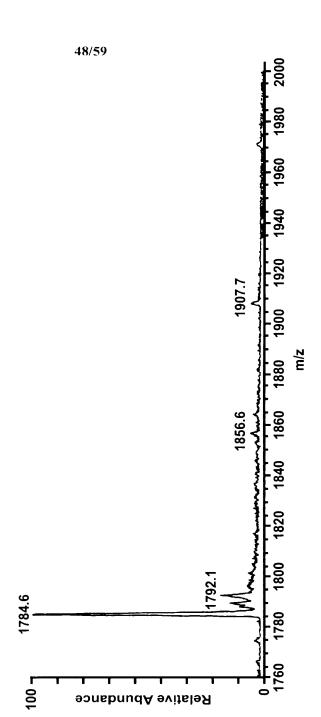


Figure 42A



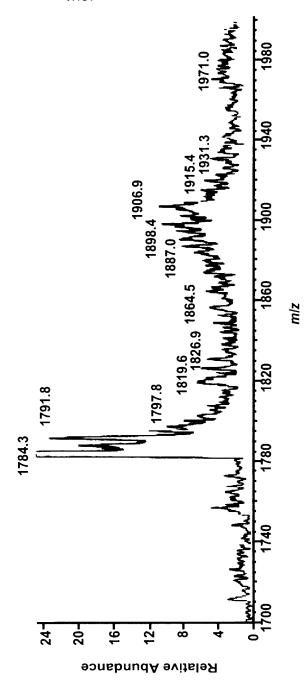
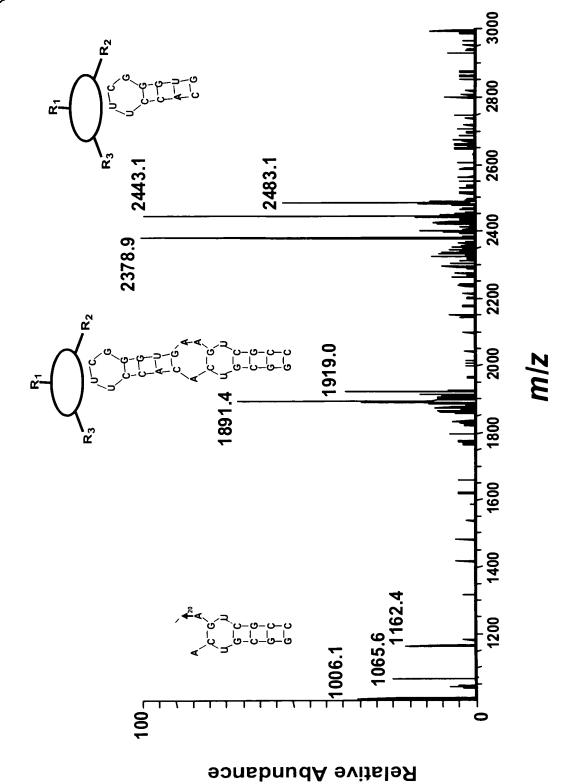


Figure 42B



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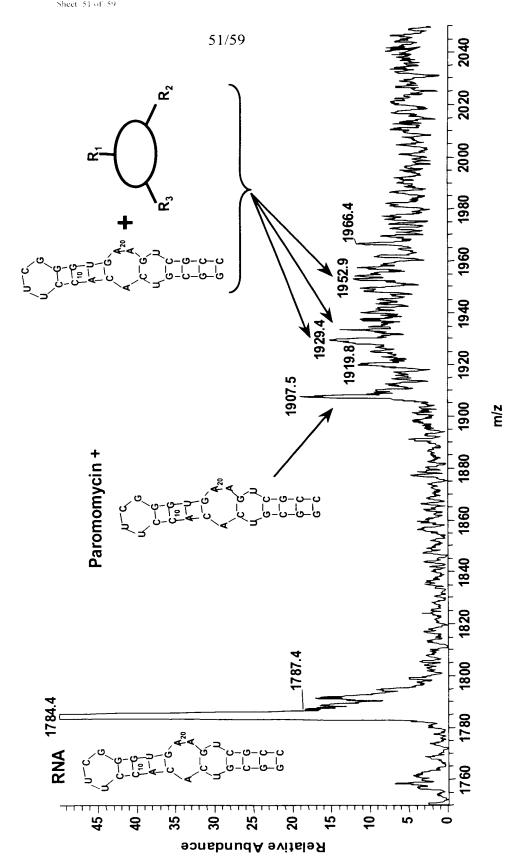


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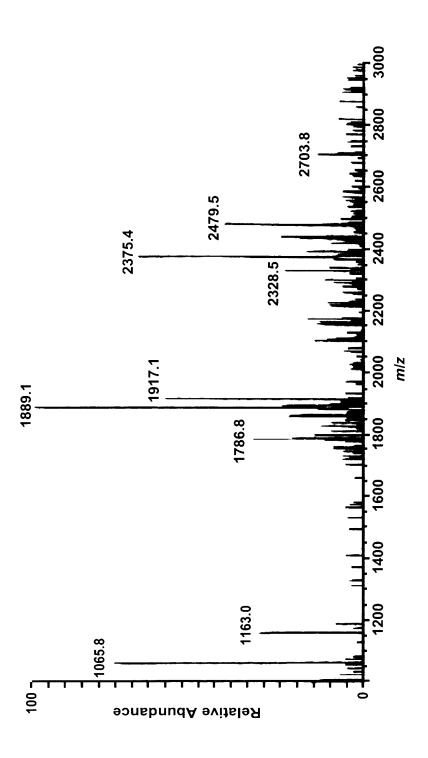


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